Stereoselective Formal Synthesis of Herbarumin III via Prins Cyclization

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Abstract: The total synthesis of herbarumin III is described, proving the versatility of the Prins cyclization in the synthesis of natural products. The approach is convergent and highly stereoselective. Ring-closing metathesis and alkene-rearrangement reactions are utilized as key steps in the synthesis of the macrocyclic lactone.

Keywords: herbarumins, Prins cyclization, alkene rearrangement, ring-closing metathesis

Herbarumin III (1) isolated\textsuperscript{14} from the fermentation broth and mycelium of the fungus Phoma herbarum displays significant phytotoxic effects against seedlings of Amaranthus hypochondriacus.\textsuperscript{15} The herbarumins macrolides 1–3 (Figure 1) interact with bovine brain calmodulin and inhibit the activation of the calmodulin-dependent enzyme cAMP phosphodiesterase. Construction of the ten-membered lactone ring and the stereocontrolled formation of the syn-1,3-diol unit are two major issues in the total synthesis of herbarumin III (1). In previous total syntheses of 1,\textsuperscript{2} the ten-membered lactone ring was synthesized by ring-closing metathesis (RCM) reaction\textsuperscript{2a,b,d} and Yamaguchi’s lactonization method.\textsuperscript{2e} Asymmetric synthesis of the syn-1,3-diol moiety has been achieved using chiral pool methods,\textsuperscript{2f} a chemoenzymatic method,\textsuperscript{2g} an asymmetric allylation/Sharpless epoxidation method,\textsuperscript{2f} and Jacobsen’s hydrolytic kinetic resolution (HKR) method.\textsuperscript{2d} Recently our group has developed a concise stereoselective total synthesis of herbarumin III utilizing Crimmins’s alid approach.\textsuperscript{2h} Herein, we describe the stereoselective synthesis of herbarumin III (1) via Prins cyclization.

The Prins cyclization has emerged as a powerful synthetic tool for the construction of multi-substituted tetrahydro-pyran systems and has been utilized in the course of the synthesis of several natural products.\textsuperscript{3} Our group has made a significant effort to explore the synthetic utility of Prins cyclization in the synthesis of various polycyclic intermediates and has utilized the Prins cyclization in the synthesis of various natural products.\textsuperscript{4} As a part of this ongoing programme, we have investigated the synthesis of herbarumin III (1).

In our retrosynthetic analysis (Scheme 1), we envisaged that the target molecule could be prepared from 15 through ring-closing metathesis. Compound 15 is viewed as being obtained from 12 via Mitsunobu inversion. It is proposed to obtain the 1,3-diol 12 from the iodide 8 via silica gel rearrangement and in turn pyran derivative 8 would be obtained via Prins cyclization of the homoallylic alcohol 4 and butyraldehyde.

In view of the importance of the macrolide 1, we have attempted its enantioselective synthesis (Scheme 2). The asymmetric total synthesis of herbarumin III (1) started with chiral homoallylic alcohol 4. Copper-mediated regioselective opening\textsuperscript{5} of benzyl (S)-glycidyl ether with vinylmagnesium bromide followed by debenzylation through treatment with lithium or sodium in liquid ammonia produced homoallylic alcohol 4. Prins cyclization of 4 with butyraldehyde in the presence of trifluoroacetic acid followed by hydrolysis of the resulting trifluoroacetate gave trisubstituted pyran.\textsuperscript{5} The stereochemistry was assumed to be in accordance as it was well examined and has been